AMX-0035 for amyotrophic lateral sclerosis (ALS) – FDA Advisory Committee update

- On September 7, 2022, the FDA convened a second Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee meeting to discuss Amylyx Pharmaceuticals' investigational drug, AMX-0035 (sodium phenylbutyrate/taurursodiol), for the treatment of amyotrophic lateral sclerosis (ALS).

- ALS is a neurodegenerative disorder characterized by the progressive degeneration and eventual death of nerve cells in the brain, brainstem, and spinal cord. Approximately 30,000 people are affected in the U.S.

- AMX-0035 a fixed-dose powder for oral suspension proposed to reduce neuronal death by simultaneously mitigating endoplasmic reticulum stress and mitochondrial dysfunction.

- The PCNS Drugs Advisory Committee previously met on March 30, 2002, to discuss the effectiveness for AMX-0035. At this prior meeting, panelists on the Committee voted 6 to 4 against the data establishing effectiveness of AMX-0035 in ALS.

    — For this meeting, Amylyx submitted data from a Phase 2, placebo-controlled study (CENTAUR) in 137 patients with ALS. The study found a statistically significant result on the primary endpoint of the slope of the ALS Functional Rating Scale-Revised (ALSFRS-R) change at 24 weeks. However, the FDA raised concerns with the statistical analysis methodology.
    — Amylyx also submitted data from an open-label extension study and reported findings of a survival benefit in patients who initially received AMX-0035 compared to those patients who originally received placebo in the CENTAUR study. FDA noted concerns about the findings given the large number of dropouts in the open-label extension period and baseline imbalances between the populations.

- Following the March Advisory Committee meeting, Amylyx submitted additional analyses of the survival data from the CENTAUR study and its open-label extension, along with biomarker results from a recently completed Phase 2 study of AMX-0035 in Alzheimer's disease.

    — A post-hoc analysis shows that the median overall survival (OS) in the intent-to-treat (ITT) AMX-0035 treatment arm (OS = 23.5 months) showed a prolongation of median OS of 9.9 months vs. the ENCALS (natural history data) predicted treatment naïve median survival (13.6 months model predicted survival, $p < 0.0001$).
    — A second post-hoc analysis estimated survival benefit using a rank-preserving structural failure time model (RPSFTM), which controls for the effect of crossover in OS results. The RPSFTM provides an estimate of the OS time for the placebo group, had treatment switching not occurred. Using this method to analyze the open-label data, the estimated median survival benefit for AMX-0035 was 9.7 months (vs. 4.8 months in the original analysis).

- An additional ongoing Phase 3, randomized, placebo-controlled trial, PHOENIX, is evaluating AMX-0035 for the treatment of ALS. The study will enroll approximately 600 patients and is expected to complete in late 2023 or early 2024 with results available shortly thereafter.

- Considering the new information submitted and the information presented at the previous PCNS meeting, the Advisory Committee was asked if the available evidence of effectiveness is sufficient to

Continued . . .

support approval of AMX-0035. Panelists could consider unmet need in ALS, the status of the ongoing Phase 3 trial, and the seriousness of ALS.

  - Despite some continued reservations with the evidence, the Committee **voted 7 to 2 in favor of approval**.
  - Those voting no cited concerns about the single trial and post-hoc nature of the confirmatory evidence.
  - Those voting yes cited the seriousness of disease, unmet need, relative safety of the drug, and additional data/analysis that appeared reassuring, albeit flawed.

- Amylyx Pharmaceuticals is expecting a final FDA approval decision for AMX-0035 by September 29, 2022.